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1 Use of prescription drugs in the older adult population

2 – a nationwide pharmacoepidemiological study

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28

29 **Abstract**

30 **Aim**

31 Multi-morbidity and polypharmacy are common among older people. It is essential to provide a
32 better understanding of the complexity of prescription drug use among older adults to optimise
33 rational pharmacotherapy. Population-based utilisation data in this age group is limited. Using the
34 Danish nationwide health registries, we aimed to characterise drug use among Danish individuals
35 ≥ 60 years.

36 **Methods**

37 This is a descriptive population-based study assessing drug prescription patterns in 2015 in the full
38 Danish population aged ≥ 60 years. The use of specific therapeutic subgroups and chemical
39 subgroups and its dependence on age were described using descriptive statistics. Profiles of drug
40 combination patterns were evaluated using latent class analysis.

41 **Results**

42 We included 1,424,775 residents (median age 70 years, 53% women). Of all the older adults, 89%
43 filled at least one prescription during 2015. The median number of drug groups used was five per
44 person. The most used single drug groups were anilides (34%), statins (33%), and platelet
45 aggregation inhibitors (24%). Eighteen drug profiles with different drug combination patterns were
46 identified. One drug profile with expected use of zero drugs and 11 drug profiles expected to receive
47 more than five different therapeutic subgroup drugs were identified.

48 **Conclusion**

49 The use of drugs is extensive both at the population level and increasing with age at an individual
50 level. Separating the population into different homogenous groups related to drug use resulted in 18
51 different drug profiles of which 11 drug profiles received on average more than five different
52 therapeutic subgroup drugs.

53

54 **What is already known about this subject**

- 55 • The use of prescription drugs is common in older people
- 56 • The use of many drugs simultaneously increases the risk of adverse drug events and drug-
- 57 drug interactions
- 58

59 **What this study adds**

- 60 • A better and updated understanding of the real-life utilisation of prescription drugs among
- 61 older adults ≥ 60 years
- 62 • An understanding of how drugs tend to compound
- 63 • Drug profiles with clinical recognisable medication profiles for the entire older population
- 64

65 **Introduction**

66 The use of prescription drugs is widespread in older people^{1,2}, and the number of drugs used is
67 increasing with age³⁻⁶. This is prompted by an increasing prevalence of multi-morbidity and
68 hospitalisations by age supplemented by a higher number of specialists who treat single diseases⁷⁻⁹.
69 Strict adherence to guidelines for each of the chronic conditions may complicate older persons'
70 pharmacotherapy and may be associated with adverse drug events¹⁰. Furthermore, the use of many
71 drugs simultaneously increases the risk of adverse drug events and drug-drug interactions^{11,12}. Due to
72 age-related changes in pharmacokinetics and pharmacodynamics, older people are at very high risk of
73 such complications^{1,5,11,13}. To this end, up to 30% of hospital admissions in older patients are related to
74 adverse drug events¹⁴⁻¹⁶. Thus, pharmacotherapy in the older adults is very complicated, and the vast
75 variety of drugs and drug combinations effect on the pharmacokinetics and pharmacodynamics and
76 makes it a difficult phenomenon to analyse.

77
78 A better and updated understanding of the real-life utilisation of prescription drugs is needed, and
79 further research is required to deepen our understanding of how drugs tend to compound and
80 interact. In addition, identifying common drug profiles, i.e. which drugs are used together, to
81 identify long-term risk drug profiles may enable health care policies, clinicians, and research fellows
82 to optimise a rational pharmacotherapy, prescribing and deprescribing patterns among older adults.
83 However, the population-based utilisation data in this age group is limited, and data are rather old.
84 Therefore, we aimed to provide a detailed study of drug use and how it changes with age to identify
85 different homogeneous drug profiles among older adults aged 60 years and older.

86
87 **Methods**

88 We performed a nationwide cross-sectional drug utilisation study in the older adult Danish population.

89
90 **Data sources**

91 Denmark has a public tax-financed health care system, which provides free and equal access
92 to primary medical care, hospitals, and home care services for all people. Patient co-payments are
93 required for prescription drugs. A central authority (the Reimbursement Committee) decides
94 whether a particular drug is reimbursable. Some prescription drugs, e.g. benzodiazepines are not
95 reimbursed¹⁷. Virtually all medical care in Denmark is furnished by the public health authorities,
96 whereby the data resources allow accurate population-based studies, covering all inhabitants of
97 Denmark.

98

99 We used data from five Danish nationwide registries; the National Prescription Registry, the Danish
100 Education Registry, the Registry for Migration, the Danish Registry of Causes of Death, and the
101 Civil Registration System. The National Prescription Registry contains full information on all
102 prescription drugs dispensed at Danish community pharmacies including prescriptions for nursing
103 home residents¹⁷. Prescriptions are coded according to the Anatomical Therapeutic Chemical (ATC)
104 classification system¹⁸. Drugs used during hospitalisation are not recorded in the register. The
105 Danish Education Register contains information on ongoing and completed education¹⁹. The
106 Register for Migration contains the date of both immigration and emigration²⁰. The Danish Register
107 of Causes of Death contains data on all deaths among people dying in Denmark²¹. The Civil
108 Registration System contains various information including sex, date of birth, and updated
109 information on vital status²². All Danish residents are recorded in the registries with a uniquely
110 personal and permanent identification number that makes it possible to crosslink individual-level
111 data across the different registries.

112

113 **Study population**

114 We included all Danish residents aged ≥ 60 years on January 1 2016. Residents who migrated during
115 2015 were excluded to ensure full follow-up data on all subjects.

116

117 **Study variables**

118 *Study drugs*

119 We retrieved information on all redeemed prescriptions in 2015. The drugs were categorised
120 according to ATC-codes into the anatomical main group (1st level), therapeutic subgroup (2nd level),
121 and chemical subgroup (4th level)¹⁸. ATC Level 1, 2, and 4 are referred to as main drug group,
122 therapeutic subgroup drug, and drug class, respectively. We defined drug users as individuals who
123 had redeemed at least one prescription of a drug class or main drug group in 2015. In the latent class
124 analysis (LCA), we disregarded the main drug group: anti-infectives for systemic use.

125

126 *Sociodemographic factors*

127 The marital status was categorised according to status on January 1 ,2016, as: married, widowed,
128 divorced or single, whereas education was categorised according to the highest attained educational
129 level at January 1 2016: short (7-10 years), medium (11-13 years) or long (≥ 14 years).

130

131 2.4 Analyses

132 First, we described baseline characteristics, i.e. sex, marital status, and education of the study
133 population. To investigate simultaneous drug use, we measured the proportion of users of 0, 1-2, 3-
134 4, 5-9, or 10+ different drug classes in 2015 stratified by age groups. Second, we determined the ten
135 most frequently used drugs classes stratified by age groups. Third, we reported the number of
136 redeemed drug classes among all residents as mean, median, interquartile range, minimum, and
137 maximum, stratified by 1-year age categories. Finally, we identified the number of residents who
138 filled at least one prescription of a main drug group in 2015. These analyses were stratified by 1-year
139 age categories.

140
141 Finally, we identified drug profiles using LCA. LCA is a method designed to identify subgroups of
142 residents who show similar patterns of behaviour, e.g. drug use²³. LCA classifies individuals into
143 mutually exclusive latent classes and assumes that given the latent class membership the use of drugs
144 is independent; thus, we used the LCA to identify different drug patterns in the general older adult
145 population. Each class identified in the LCA will thus have similar drug patterns and therefore have
146 the same drug profile. To reduced computer running time we selected five random samples of our
147 population, each with 50,000 residents. For the same reason, we chose drugs at therapeutic
148 subgroup level instead of drug classes. To avoid too few observation, the drugs were identified as
149 the 95% most used drugs in 2015. Thus, the LCA was based on drugs from 28 therapeutic
150 subgroups. Moreover, this made it possible to investigate the consistency of the drug profiles
151 identified in five random samples. The number of drug profiles was estimated in an iterative process
152 starting with a model with a two LCA class solution and continuing up to 20 LCA classes for each
153 of the five datasets. To measure the relative fit of the models, which refers to the adequacy of one
154 model's representation of data compared with that of another model, we used the Bayesian
155 Information Criterion (BIC)²⁴. This was used together with substantive interpretability and clinical
156 judgment to determine the number of drug profiles for each of the five datasets²⁵. Afterwards, the
157 optimal number of drug profiles and parameter estimates were compared for the five datasets, and
158 the final number of drug profiles was decided. The entropy-based pseudo-R² measure can
159 summarise the association between the drug profiles. The values 0.36, 0.65, and 0.90 represent low-,
160 medium-, and high-separation conditions, respectively²⁶. Posterior probabilities for drug profile
161 membership were calculated for all residents in the cohort using the average parameter estimates
162 from the five datasets. All residents were assigned to a specific drug profile based on modal
163 assignment (the drug profile with the highest posterior probability). The distribution of sex and the

164 median for age were performed for each drug profile. To account for local maxima of the likelihood
165 function for LCA we initially used 450 randomly generated starting values. If the best likelihood
166 were not replicated, then the number of starting values was increased.

167

168 **Ethics and reporting**

169 The study was approved by the Scientific Board of Statistics Denmark and the Danish Data
170 Protection Agency (ref. 00003115). An approval from an ethics committee is not required for
171 registry-based studies in Denmark. No identifiable patient data could be retrieved. The study was
172 conducted by following the Strengthening the Reporting of Observational Studies in Epidemiology
173 (STROBE) recommendations²⁷.

174 **Results**

175 **Drug use**

176 We identified 1,424,775 residents aged ≥ 60 years in Denmark in 2015. The female proportion was
177 53%. The median age of the population was 70 years (interquartile range (IQR) 65-77, range 60 to 110)
178 without differences across sex (70 years for men and 71 years for women). The most used single drug
179 classes measured by the number of unique users were anilides (34%), statins (33%), platelet aggregation
180 inhibitors (24%), proton pump inhibitors (21%), and calcium channel blockers (20%). (Table 1).

181
182 Of all the older adults, 89% filled at least one prescription during 2015. The median number of unique
183 drug classes filled was five per person (IQR, 2-8), similar for men and women (four drug classes (IQR,
184 2-8) and five drug classes (IQR, 2-9), respectively). We observed a trend toward an increasing number
185 of prescribed drug classes by age. However, with a levelling off around age 90 (Figure 1).

186
187 Cardiovascular drugs were the most used main drug group ($1 \geq$ prescription filled by 62% of all
188 residents), followed by drugs related to the nervous system (48%), alimentary tract and metabolism
189 (38%), anti-infectives for systemic use (35%), and blood and blood-forming organs (34%). This was
190 largely consistent across age (Figure 2), although with a tendency towards a slightly increased
191 proportion of drugs related to blood and blood-forming organs was observed whereas the
192 proportion of drugs related to the genitourinary system and sex hormones decreased slowly by age.

193

194 **Drug profiles**

195 By using the drugs from the 28 covering 95% of all drug groups used in 2015, we fitted up to a 20
196 LCA class model. Looking at model fit, the BIC was lowest in the model with 19-drug profiles for
197 four datasets and in the model with 18 drug profiles for one dataset. When comparing the
198 therapeutic subgroup drug probabilities within each drug profile among the five different datasets
199 for the 19-drug profile models, two of the 19-drug profiles were very differently estimated, showing
200 no consistency among the datasets in how to identify them. However, for the 18-drug profile model,
201 the results were similar (Appendix 1). Since no consistent pattern was obtained in the 19-drug
202 profile model, and with a clinical judgment by a clinical difference in the drug profiles we used the
203 18-drug profile model as our final model. Moreover, the mean entropy-based pseudo- R^2 measure
204 was in our study 0.67 (range: 0.66-0.68), placing the separation of the 18 drug profiles as medium-
205 separation conditions.

206

207 Table 2 shows the conditional probabilities of the 28 therapeutic subgroup drugs in the 18 identified
208 drug profiles and the relationship between age and sex for each drug profile. Multiple drug use was
209 in this study defined as receiving drugs from five or more different therapeutic subgroup drugs.
210 Multiple drug use was observed in 11 drug profiles (drug profile 1 to 11). Two of these drug profiles
211 had a considerable overlap (drug profile 1 and 4). Thus, one drug profile (drug profile 1) consisted
212 of high probabilities for all 28 therapeutic subgroup drugs and was characterised by the highest
213 expected numbers of therapeutic subgroup drugs whereas the other drug profile (drug profile 4) had
214 a high probability of receiving all therapeutic subgroup except for mineral supplements and
215 diuretics. The second highest number of expected therapeutic subgroup drugs was observed in
216 combination with the highest median age, and the highest proportion of females. The probability of
217 receiving a drug for both the cardiovascular system, alimentary tract and metabolism, and for the
218 blood and blood-forming organs were characterised for drug profile 1-7. An expected number of
219 different therapeutic subgroup drugs under five were characterised for drug profile 12-18. The
220 highest proportion of males was found in drug profile 12. Similar, drug profile 16 was characterised
221 by low probability of receiving drugs except for hypertensive drugs. Drug profile 18 was the largest.
222 It had a prevalence of 21% and consisted of those with a probability of zero or very close to zero
223 for receiving any drug from the different included therapeutic subgroup drugs. The median age for
224 residents in drug profile 18 was the lowest among the 18 drug profiles at 67 years old, and the sex
225 ratio was also almost 1:1. Thus, the most prevalent drug profiles characterised by expected multiple
226 drug use were drug profile 1-6 (11.2-7.6 expected therapeutic subgroup drugs) and had a total
227 prevalence of 19%. To characterise the different therapeutic subgroup drugs used in LCA we have
228 listed the three most frequent drug classes at the 28 different therapeutic subgroup drugs in
229 Appendix 2.

230 **Discussion**

231 In this cross-sectional nationwide drug utilisation study, we investigated prescribing patterns and
232 drug combination profiles in older adults in Denmark in 2015. Our study showed that extensive
233 drug use among older adults was very common. Older people aged ≥ 60 years, redeemed drugs from
234 five (median) different drug classes at the pharmacy each year. The number of redeemed drugs
235 increased by age from a median level at 4 for persons between 60 and 69 years old to a median level
236 at 8 for older people aged ≥ 80 years. However, the distribution of drugs from main groups was
237 almost stable across age groups. Further, we identified 18 different drug profiles; one drug profile
238 with a low probability of receiving any drugs, which included 21 % of the population ≥ 60 , and 11
239 drug profiles, which on average received drugs from more than five different therapeutic subgroups.
240

241 Our study investigated current drug use among older adults in Denmark and showed that drug
242 consumption is well within the range of previous studies. Previous studies were, however, primarily
243 based on selected populations and fairly old data sets. To our knowledge, no other studies have
244 included the entire Danish population ≥ 60 years. A Swedish study showed that older adults (≥ 65) used
245 an average of 4.6 different drugs (ATC level 5)²⁸ whereas, a Danish study found that the median
246 number of drugs among residents ≥ 60 years was 5 (IQR: 2-9) (ATC level 5)²⁹. We confirmed the
247 findings from Linjakumpu et al.³ that the number of drugs increased by age. However, the increase in
248 the number of redeemed drug classes seems larger in our study. One reason for this might be the larger
249 population and the general increase in drug consumption. Similar to our findings, Lagerin et al.³⁰
250 reported that the number of drugs at ATC level 3 stabilised at the age of 85-90. This stabilisation of the
251 drug use can be expected because the increased life expectancy in the older population has raised the
252 prevalence of multi-morbidity³¹, and the number of drugs was highly correlated with the number of
253 chronic conditions²⁸. The impact of evidence-based clinical guidelines for the treatment of the specific
254 disease may also contribute to the observed increase in drug use³². This can be explained by the fact
255 that each guideline has several recommended drugs and the majority of older people are multimorbid.
256

257 We found that cardiovascular drugs were the most commonly used main drug group, which is in
258 accordance with previous findings. Barat et al. found that the two most common prescription drugs
259 among 75-years-old community-dwelling residents were cardiovascular drugs (25%) and central
260 nervous system drugs (23%)³³. In a Swedish study among older adults ≥ 78 years of age, cardiovascular
261 drugs were also the most frequently used drugs followed by nervous system drugs, and alimentary tract
262 metabolism drugs³². Similar results were found by Wastesson et al.³⁴. We further found that the

distribution of main drug groups was stable over age, which indicates that the drug patterns do not change significantly with age and suggest that drugs may not be discontinued in late life.

A complex drug burden is potentially harmful to the patients and difficult to manage^{10,35}. The drug burden is often measured by the number of different drugs used but ignoring the complexity of the drug profiles. To our knowledge, LCA has never been performed in a large, national population, and with therapeutic subgroup drugs as outcomes. In previous studies, LCA has been used to define, e.g., subtypes of drug abuse in a Swedish cohort (n=192,501)³⁶ and to identify patterns of drug use associated with lower serum sodium concentration in older hospitalised patients (n=101)³⁷. In both studies, the drugs were selected to fit a selected patient group, and the analysis included only a limited number of drugs or drug classes, whereas only three and six different drug profiles were identified. In this study 18-drug profiles, i.e. clinical recognisable medication patterns were identified. For example, drug profile 13 is characterised by a high probability of receiving drugs for diabetes, agents acting on the renin-angiotensin system, and lipid-modifying agents. In general, the drug profiles demonstrated very complex therapeutic profiles and reflecting the high level of multimorbidity. However, the drug profiles should be explored more thoroughly to fit the clinical practice, e.g. to risk-stratified patients in a hospital or a general practice. When identifying drug profiles, LCA is considered highly suitable because the drug groups differ qualitatively from each other. Also, we found similar drug profiles for the five randomly selected samples which indicates that the 18 drug profiles are very stable. The drug profiles allow us to study drug use and drug combinations in a new way. By using the drug profiles, it is possible to identify in which of the drug profiles a given drug is used, and thereby restrict studies of adverse effects to individuals with different drug combination profiles. Real word evidence in different drug profiles makes the result more usable in clinical practice. We believe that the new method is important also when studying drug channelling bias in more sufficient ways, and when studying polypharmacy more comprehensively.

Strengths and limitations

Our study is the first study investigating drug profiles in a large population using LCA. The use of LCA in an unselected population enables a nuanced identification and description of drug profiles. More in-depth knowledge of the drug patterns is desired, e.g. studying drug profiles at drug class level instead of at therapeutic subgroup level. This was, however, not possible in this study due to the lack of computer power. In future studies, drug profiles have the potential to be evaluated on drug class level, to achieve knowledge on among other drug safety, interactions, adverse drug events,

maybe by investigating individuals with a specific drug profile. Another strength of this study is that data were obtained from nationwide registers containing high-quality data. This ensures complete coverage and eliminates the risk of selection bias.

A limitation of this study is that certain drugs can be purchased over the counter in Denmark and drug, therefore, can be slightly underestimated. Olesen et al.³⁸ found that 28 percent of the patients aged 65 years or more used non-prescription drugs. Indeed, the majority are prescription drugs, especially with respect to the most potent drugs and those with the greatest potential of interactions. Another potential limitation is that we had no information on drug adherence among older adults. Though we know the older adults have filled the prescription, we do not know whether the older adults have taken the drug. At the same time, we eliminate primary non-adherence, which is a strength. We required at least one prescription for all drugs in the analyses, though we did not know if the older adults were compliant to the given drug. Due to the excessive computer running time, we were further compelled to reduce the population to five random samples of 50,000 individuals each. We assume a sample of 50,000 individuals as a large population, and that the results would not be different compared with the final population.

In conclusion, we found that the use of drugs is extensive both at the population level and at the individual level and that it is increasing with age. Cardiovascular drugs, analgesics and psychotropic drugs were the most prevalent drug classes. Eighteen different drug profiles were identified, 11 drug profiles reflecting probable drug combination profiles among users of multiple drug use. The identified drug profiles described clinical recognisable medication patterns. The drug profiles have the potential to be used in future studies investigating high-risk prescriptions patterns. Studies of the older adult population with diverging drug profiles may provide useful information to prevent drug-related problems and optimise drug treatment. For instance, with more research into risk patterns, we can produce risk profiles that will provide a better understanding of which patients benefit most from medication review. Furthermore, these risk profiles may also benefit the patients when a new medication is added to the treatment for a more rational drug prescribing.

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331

332 **Author Contributions**

333 Christensen, Juul-Larsen, Petersen have full access to all the data in the study and takes responsibility
334 for the integrity of the data and the accuracy of the data analysis. Study concept and design:
335 Christensen, Pottegård, Petersen. Acquisition, analysis, or interpretation of data: Christensen,
336 Pottegård, Petersen. Drafting of the manuscript: All authors. Critical revision of the manuscript for
337 important intellectual content: All authors. Statistical analysis: Christensen, Petersen. Administrative,
338 technical, or material support: Petersen. Study supervision: Kaae, Andersen, Pottegård, Petersen.

339

340 **Conflict of Interest Disclosures**

341 There are no competing interests to declare.

342

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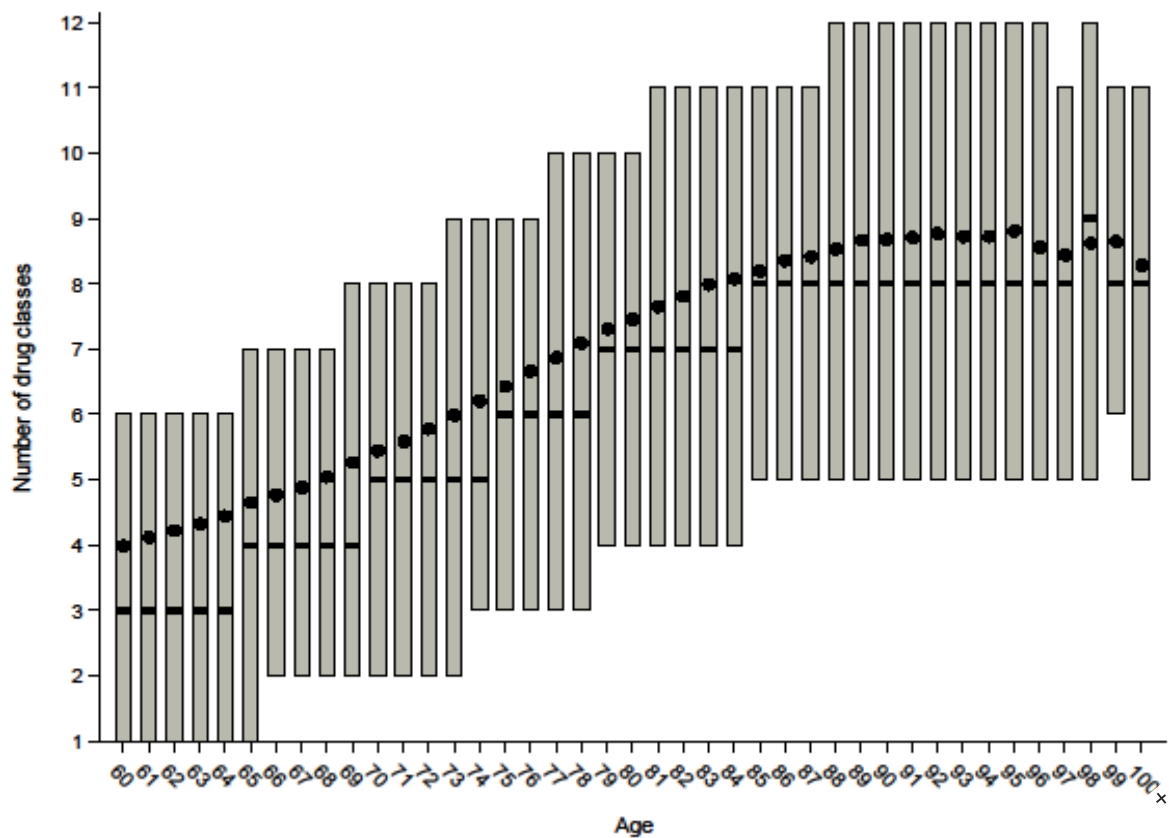
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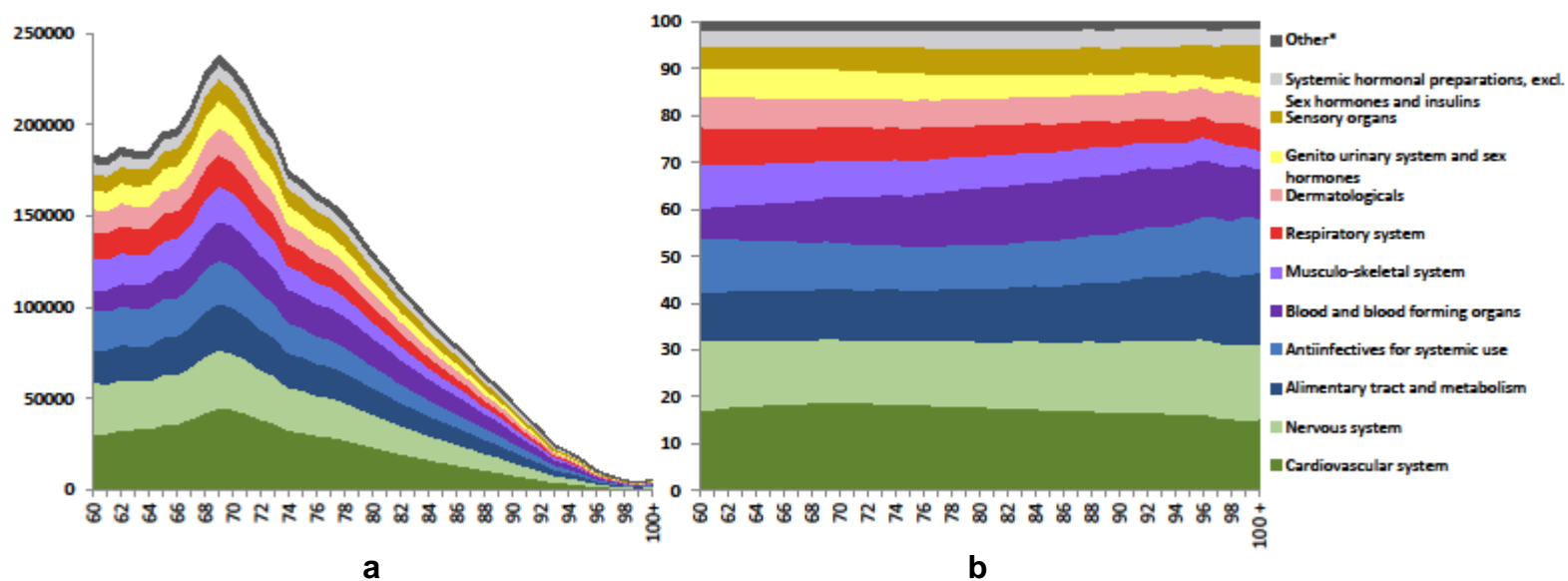
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1
2 **Figure 1: Number of unique drug classes depicted as a function of age.**
3 Boxes represent the interquartile range with the median score shown as a horizontal line and the
4 means represented as circles.

1



2

3

4 **Figure 2 Parts a-b: Overall distribution of drugs used.**

5 2A: Number of main drug groups stratified by age. 2B: Percentage of main drug groups stratified by age.

6

1 Table 1. Demographic and drug characteristics.

Characteristic	Age groups (year)			
	Total No. (%)	60-69 No. (%)	70-79 No. (%)	80+ No (%)
	1424775	688623 (48.3)	490295 (34.4)	245857 (17.3)
Sociodemographic characteristics				
Female sex	759255 (53.3)	348609 (50.6)	258311 (52.7)	152335 (62.0)
Marital status				
Married ^a	842138 (59.1)	456828 (66.3)	300875 (61.4)	84435 (34.3)
Widowed	274533 (19.3)	48189 (7.0)	96843 (19.75)	129501 (52.7)
Divorced	201153 (14.1)	112102 (16.3)	68038 (13.9)	21013 (8.6)
Single	106951 (7.5)	71504 (10.4)	24539 (5.0)	10908 (4.4)
Highest achieved education^b				
Short (7-10 years)	498173 (36.0)	185095 (27.4)	186750 (39.2)	126328 (54.9)
Medium (11–12 years)	551070 (39.9)	294205 (43.6)	188201 (39.5)	68664 (29.8)
Long (≥13 years)	333118 (24.1)	195837 (29.0)	102088 (21.4)	35193 (15.3)
Medication				
Median number drug classes (IQR ^c)	5 (2-8)	4 (1-7)	5 (3-9)	8 (4-11)
Number of simultaneously used drugs classes				
0	155,692 (10.9)	105,130 (15.3)	40,986 (8.4)	9,576 (3.9)
1-2	253,138 (17.8)	157,282 (22.8)	76,033 (15.5)	19,823 (8.1)
3-4	264,930 (18.6)	141,372 (20.5)	90,590 (18.5)	32,968 (13.4)
5-9	477,536 (33.5)	201,525 (29.3)	178,395 (36.4)	97,616 (39.7)
10+	273,479 (19.2)	83,314 (12.1)	104,291 (21.3)	85,874 (34.9)
10 most frequent drugs classes				
Anilids ((N02BE)	483,772 (34.0)	184,981 (26.9)	173,338 (35.4)	125,453 (51.0)
HMG CoA reductase inhibitors (C10AA)	466,062 (32.7)	190,265 (27.6)	189,804 (38.7)	85,993 (35.0)
Platelet aggregation inhibitors excl. heparin (B01AC)	337,985 (23.7)	109,735 (15.9)	134,318 (27.4)	93,932 (38.2)
Proton pump inhibitors (A02BC)	295,668 (20.8)	120,132 (17.4)	108,428 (22.1)	67,108 (27.3)
Dihydropyridine derivatives (C08CA)	285,250 (20.0)	107,662 (15.6)	110,412 (22.5)	67,176 (27.3)
Beta blocking agents, selective (C07AB)	241,009 (16.9)	82,228 (11.9)	94,658 (19.3)	64,123 (26.1)
Propionic acid derivatives (M01AE)	229,475 (16.1)	120,989 (17.6)	78,864 (16.1)	29,622 (12.0)
ACE inhibitors, plain (C09AA)	206,732 (14.5)	80,935 (11.8)	79,301 (16.2)	46,496 (18.9)
Beta-lactamase sensitive penicillins (J01CE)	199,701 (14.0)	94,581 (13.7)	67,817 (13.8)	37,303 (15.2)
Thiazides and potassium in combination (C03AB)	185,262 (13.0)	65,308 (9.5)	71,188 (14.5)	48,766 (19.8)

2 ^a Includes registered partnership

3 ^b Missing: 42,414 people

4 ^c IQR= interquartile range

1

2 Table 1: The conditional probabilities of the 28 therapeutic subgroup drugs in the 18 identified drug profiles.

Profile	P ^a	1	2	3	4	5	6	7	8
Profile size, No (%)		42,743 (3)	28,496 (2)	56,991 (4)	56,991 (4)	42,743 (3)	42,743 (3)	71,239 (5)	42,743 (3)
Age, median (IQR)	70 (62-77)	78 (71-84)	81 (72-89)	78 (71-84)	75 (69-82)	75 (68-82)	71 (66-77)	72 (68-78)	73 (66-81)
Sex, female (%)	53.3	62.5	72.7	48.7	49.7	61.1	68.6	36.1	74.9
Expected number of therapeutic subgroup drugs		11.2	8.3	8.1	7.6	7.6	7.2	6.7	6.7
Therapeutic subgroup drug									
A02: Drugs for acid related disorders	22%	72%	60%	30%	49%	45%	43%	20%	62%
A06: Drugs for constipation	5%	29%	43%	6%	12%	22%	2%	1%	25%
A10: Drugs used in diabetes	11%	34%	5%	20%	16%	28%	11%	55%	2%
A12: Mineral supplement	10%	63%	74%	59%	0%	16%	8%	18%	2%
B01: Antithrombotic agents	30%	90%	43%	99%	100%	62%	28%	77%	17%
B03: Antianemic preparations	6%	25%	22%	9%	13%	17%	5%	11%	14%
C01: Cardiac Therapy	6%	38%	12%	46%	33%	3%	3%	8%	2%
C03: Diuretics	23%	91%	91%	96%	12%	36%	37%	48%	18%
C07: Beta blocking agents	20%	59%	22%	81%	55%	25%	21%	55%	10%
C08: Calcium channels blockers	21%	41%	24%	33%	33%	39%	32%	62%	12%
C09: Agents acting on the renin-angiotensin system	36%	60%	27%	66%	47%	62%	59%	96%	20%
C10: Lipid modifying agents	33%	76%	15%	64%	73%	73%	45%	91%	16%
D07: Topical dermatological Corticosteroids	13%	26%	22%	15%	21%	16%	35%	13%	23%
G03: Sex hormones and modulators of the genital system	10%	17%	14%	6%	13%	10%	26%	3%	26%
G04: Urologicals	10%	16%	11%	13%	18%	14%	12%	14%	11%
H02: Corticosteroids for system use	6%	27%	19%	8%	12%	0%	19%	2%	17%
H03: Thyroid therapy	6%	14%	12%	10%	8%	11%	10%	5%	11%
M01: Antiinflammatory and antirheumatic products	19%	25%	23%	10%	24%	19%	32%	11%	46%
M05: Drugs for treatment of bone diseases	6%	16%	19%	6%	11%	8%	8%	1%	16%
N02: Analgesics	38%	94%	89%	53%	76%	73%	63%	31%	97%
N03: Antiepileptics	5%	20%	17%	3%	10%	20%	4%	3%	23%
N04: Anti-parkinson drugs	2%	6%	6%	1%	3%	7%	2%	0%	7%
N05: Psycholeptics	15%	45%	42%	16%	30%	46%	28%	6%	55%
N06: Psychoanaleptics	13%	40%	44%	11%	22%	61%	15%	8%	48%
R01: Nasal preparations	6%	11%	5%	4%	9%	2%	41%	3%	13%
R03: Drugs for obstructive airways diseases	13%	41%	29%	19%	22%	13%	43%	7%	25%
R06: Antihistamines for systemic use	6%	17%	12%	4%	11%	6%	43%	3%	19%
S01: Ophthalmologicals	17%	31%	29%	18%	26%	23%	48%	17%	31%

Profile	9	10	11	12	13	14	15	16	17	18
Profile size, N (%)	71239 (5)	28,496 (2)	71,239 (5)	113,982 (8)	56,991 (4)	1,245 (0.1)	128,230 (9)	156,725 (11)	99,734 (7)	299,203 (21)
Age, median (IQR)	71 (66-77)	74 (68-81)	74 (68-82)	72 (68-79)	70 (65-75)	69 (64-75)	68 (64-74)	70 (65-75)	69 (64-74)	67 (63-72)
Sex, female (%)	55.1	69.2	75.3	34.7	39.0	63.8	60.8	50.2	62.7	49.0
Expected number of therapeutic Subgroup drugs	6.4	5.2	5.1	4.3	4.2	3.3	3.0	2.9	2.8	0.5
Therapeutic subgroup drug										
A02: Drugs for acid related disorders	41%	33%	18%	13%	14%	17%	25%	10%	18%	3%
A06: Drugs for constipation	4%	5%	2%	0%	1%	7%	3%	0%	1%	0%
A10: Drugs used in diabetes	18%	4%	7%	3%	56%	2%	1%	3%	1%	1%
A12: Mineral supplement	7%	7%	41%	1%	0%	0%	0%	4%	0%	0%
B01: Antithrombotic agents	35%	30%	24%	97%	34%	10%	3%	7%	4%	1%
B03: Antianemic preparations	6%	16%	6%	3%	8%	7%	4%	2%	4%	1%
C01: Cardiac Therapy	1%	1%	1%	13%	0%	1%	0%	1%	1%	0%
C03: Diuretics	32%	20%	100%	12%	8%	6%	5%	21%	4%	1%
C07: Beta blocking agents	23%	10%	30%	47%	4%	8%	3%	17%	2%	1%
C08: Calcium channels blockers	43%	23%	33%	25%	21%	8%	4%	43%	4%	1%
C09: Agents acting on the renin-angiotensin system	72%	33%	43%	42%	69%	14%	11%	68%	10%	4%
C10: Lipid modifying agents	55%	28%	31%	66%	85%	16%	7%	28%	11%	4%
D07: Topical dermatological Corticosteroids	14%	8%	15%	10%	10%	12%	11%	10%	22%	5%
G03: Sex hormones and modulators of the genital system	12%	11%	14%	4%	4%	15%	13%	7%	19%	5%
G04: Urologicals	14%	7%	4%	14%	14%	7%	9%	10%	10%	4%
H02: Corticosteroids for system use	6%	52%	4%	2%	2%	1%	5%	1%	10%	0%
H03: Thyroid therapy	6%	10%	12%	4%	6%	9%	4%	4%	7%	2%
M01: Antiinflammatory and antirheumatic products	71%	18%	16%	7%	14%	8%	58%	9%	10%	4%
M05: Drugs for treatment of bone diseases	4%	43%	7%	3%	2%	7%	6%	3%	8%	2%
N02: Analgesics	100%	60%	42%	20%	22%	35%	78%	13%	17%	3%
N03: Antiepileptics	7%	3%	2%	2%	1%	11%	3%	1%	1%	0%
N04: Anti-parkinson drugs	2%	2%	1%	1%	1%	5%	1%	0%	0%	0%
N05: Psycholeptics	18%	14%	12%	5%	5%	46%	10%	5%	9%	1%
N06: Psychoanaleptics	9%	15%	8%	5%	7%	45%	5%	4%	5%	1%
R01: Nasal preparations	5%	0%	2%	4%	3%	2%	4%	3%	23%	1%
R03: Drugs for obstructive airways diseases	11%	44%	12%	7%	7%	7%	9%	6%	26%	2%
R06: Antihistamines for systemic use	5%	0%	4%	2%	3%	3%	3%	2%	18%	0%
S01: Ophthalmologicals	16%	19%	18%	13%	14%	16%	12%	12%	30%	7%

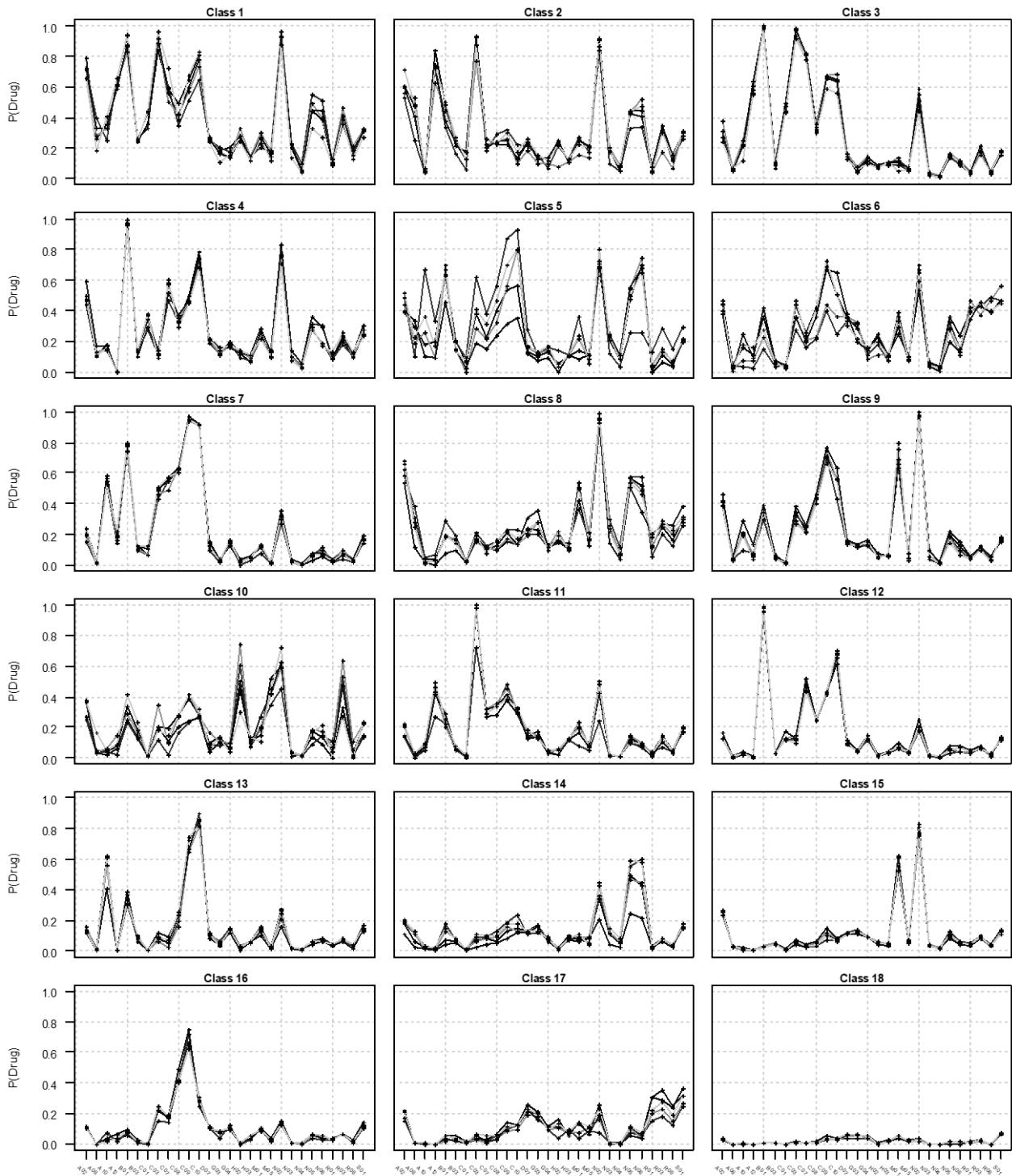
3 ^a=probability of receiving the therapeutic subgroup drug in general

4 Bold: 25% Increase of the overall probability. The colored boxes: Increase of at least 10 percent points over the overall probability. Different colors represent

5 different main groups

1 Appendix 1:

2 Supplement to: Use of prescription drugs in the older adult population – a nationwide
3 pharmacoepidemiological study. Christensen LD*, Reilev M, Juul-Larsen HG, Jørgensen LM, Kaae
4 S, Andersen O, Pottegård A, Petersen J. *Corresponding author: Clinical Research Center,
5 Copenhagen University Hospital Hvidovre, Denmark, Kettegaard Allé 30, 2650 Hvidovre,
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7
8 Figure 3. 18 drug profile model. Five datasets with 50,000 individuals for each class.

1 Appendix 2:

2 Supplement to: Use of prescription drugs in the older adult population – a nationwide pharmacoepidemiological
3 study. Christensen LD*, Reilev M, Juul-Larsen HG, Jørgensen LM, Kaae S, Andersen O, Pottsgård A, Petersen J.
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8 **Table 3. Three most frequent drug classes in the 28 therapeutic subgroup drugs used for the Latent Class Analysis**

Therapeutic subgroup drugs	Drug classes
A02: Drugs for acid related disorders	A02BC: proton pump inhibitors, A02AA: magnesium compounds, A02AD: combinations and complexes of aluminium, calcium and magnesium compounds
A06: Drugs for constipation	A06AD: Osmotically acting laxatives, A06AB: Contact laxatives, A06AG: Enemas
A10: Drugs used in diabetes	A10BA: Biguanides, A10BB: Sulfonylureas, A10AE: Insulins and analogues for injection, long-acting
A12: Mineral supplement	A12BA: Potassium, A12AA: Calcium, A12AX: Calcium, combinations with vitamin D and/or other drugs
B01: Antithrombotic agents	B01AC: Platelet aggregation inhibitors excl. heparin, B01AA: Vitamin K antagonists, B01AF: Direct factor Xa inhibitors
B03: Antianemic preparations	B03BA: Vitamin B12 (cyanocobalamin and analogues), B03BB: Folic acid and derivatives, B03AA: Iron bivalent, oral preparations
C01: Cardiac Therapy	C01DA: Organic nitrates, C01AA: Digitalis glycosides, C01BD: Antiarrhythmics, class III
C03: Diuretics	C03AB: Thiazides and potassium in combination, C03CA: Sulfonamides, plain, C03DA: Aldosterone antagonists
C07: Beta blocking agents	C07AB: Beta blocking agents, selective, C07AG: Alpha and beta blocking agents, C07AA: Beta blocking agents, non-selective
C08: Calcium channels blockers	C08CA: Dihydropyridine derivatives, C08DA: Phenylalkylamine derivatives, C08DB: Benzothiazepine derivatives
C09: Agents acting on the renin-angiotensin system	C09AA: ACE inhibitors, plain, C09CA: Angiotensin II antagonists, plain, C09DA: Angiotensin II antagonists and diuretics
C10: Lipid modifying agents	C10AA: HMG CoA reductase inhibitors, C10AX: Other lipid modifying agents, C10AB: Fibrates
D07: Topical dermatological Corticosteroids	D07AC: Corticosteroids, potent (group III), D07AB: Corticosteroids, moderately potent (group II), D07AD: Corticosteroids, very potent (group IV)
G03: Sex hormones and modulators of the genital system	G03CA: Natural and semisynthetic estrogens, plain, G03FA: Progestogens and estrogens, fixed combinations, G03FB: Progestogens and estrogens, sequential preparations
G04: Urologicals	G04BE: Drugs used in erectile dysfunction, G04CA: Alpha-adrenoreceptor antagonists, G04BD: Drugs for urinary frequency and incontinence
H02: Corticosteroids for system use ^a	H02AB: Glucocorticoids, H02AA: Mineralocorticoids
H03: Thyroid therapy	H03AA: Thyroid hormones, H03BB: Sulfur-containing imidazole derivatives, H03BA: Thiouracils
M01: Antiinflammatory and antirheumatic products	M01AE: Propionic acid derivatives, M01AB: Acetic acid derivatives and related substances, M01AX: Other antiinflammatory and antirheumatic agents, non-steroids
M05: Drugs for treatment of bone diseases	M05BA: Bisphosphonates, M05BX: Other drugs affecting bone structure and mineralization, M05BB: Bisphosphonates, combinations
N02: Analgesics	N02BE: Anilids, N02AX: Other opioids, N02AA: Natural opium alkaloids
N03: Antiepileptics	N03AX: Other antiepileptics, N03AF: Carboxamide derivatives, N03AG: Fatty acid derivatives
N04: Anti-parkinson drugs	N04BC: Dopamine agonists, N04BA: Dopa and dopa derivatives, N04BD: Monoamine oxidase B inhibitors
N05: Psycholeptics	N05CF: Benzodiazepine related drugs, N05BA: Benzodiazepine derivatives, N05AH: Diazepines, oxazepines, thiazepines and oxepines
N06: Psychoanaleptics	N06AA: Non-selective monoamine reuptake inhibitors, N06AB: Selective serotonin reuptake inhibitors, N06AX: Other antidepressants
R01: Nasal preparations	R01AD: Corticosteroids, R01AX: Other nasal preparations, R01AA: Sympathomimetics, plain
R03: Drugs for obstructive airways diseases	R03AC: Selective beta-2-adrenoreceptor agonists, R03AK: Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics, R03BB: Anticholinergics
R06: Antihistamines for systemic use	R06AX: Other antihistamines for systemic use, R06AE: Piperazine derivatives, R06AD: Phenothiazine derivatives
S01: Ophthalmologicals	S01AA: Antibiotics, S01XA: Other ophthalmologicals, S01CA: Corticosteroids and antiinfectives in combination

